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The Synthesis of Asimilobin and the Correction of Its Tetrahydrofuran Segment's Configuration

Zhi-Min Wang,* Shi-Kai Tian and Min Shi*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences 354 Fenglin Lu, Shanghai 200032, China

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Abstract

A highly efficient synthetic method for the *trans/threo/trans-* bis-tetrahydrofuran (THF) ring building block was established. The title compound was synthesized in thirteen steps from *trans-*1,4-dichloro-2-butene *via* a convergent route with a Wittig reaction as the key step. The absolute configuration of the THF segment of naturally occurring asimilobin should be corrected. © 1999 Elsevier Science Ltd. All rights reserved.

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In recent years, the rapidly growing class of naturally occurring Annonaceous acetogenins has received considerable attention, due to their broad spectrum of biological activity such as cytotoxic, antitumor, antimicrobial, antimalarial, antifeedant, pesticidal and immunosuppressive effects.¹ Asimilobin, a relatively rare bulladecin type acetogenin,¹ was isolated by McLaughlin's group both from the seeds of *Asimina triloba*² and the bark of *Goniothalamus giganteus* (Annonaceae),³ and showed cytotoxicity values comparable with adriamycin against six human solid tumor cell lines. Its absolute configuration has been determined to be 1 by spectroscopic analysis (Figure 1). The striking characteristics are the adjacent *threo/trans/threo/trans* bis-THF ring and one flanking hydroxyl group at the α -position of THF core.

Although several total syntheses of adjacent bis-THF acetogenins bearing two flanking hydroxyl groups at the α, α' -positions have been reported,⁴⁻⁸ no successful synthesis of those bis-THF acetogenins with only one flanking hydroxyl group has been achieved to date. Herein we wish to report our facile route to the first total synthesis of asimilobin.



We had developed a highly efficient and stereocontrolled synthetic method to construct the *trans/threo/trans* bis-THF ring building block 2 in three steps (Scheme 1). Sharpless AD ⁹ reaction on the starting material 3 installed the two stereogenic centers, with greater than 94% ee, ¹⁰ in the bis-THF ring backbone. The resulting diol 4 was subsequently treated with NaH and allylmagnesium chloride in the presence of CuI to produce compound 5 in 79% yield. This was smoothly oxidized and cyclized to form a C₂-symmetrical bis-THF compound 2 in 78% yield using Co(modp)₂ [bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentane-dionato) cobalt(II)] ¹¹ as a catalyst under an oxygen atmosphere. Compound 2 was confirmed to have 96% de by GC/MS analysis of its dimethyl ether derivative. To the best of our knowledge, this synthetic route is much shorter and more convenient than that reported in the literature ¹² so far.



Conditions: a) $K_3Fe(CN)_{6}$, K_2CO_3 , NaHCO₃, MeSO₂NH₂, (DHQ)₂PHAL, $K_2OsO_2(OH)_4$, ¹BuOH:H₂O (1:1), 0 °C; 84%. b) 1) NaH, THF 2) allylmagnesium chloride, Cul, THF, -50°C; 79%. c) Co(modp)₂, TBHP, O₂, *i*-PrOH; 78%. d) NaH, BnBr, THF; 71%. e) Swem oxidation. f) CH₃(CH₂)₁₃MgCl, CuBr:SMe₂, Et₂O, -78 -0 °C; 49% (two steps). g) MOMCl, *i*-Pr₂NEt, CH₂Cl₂;87%. h) H₂, Pd/C, EtOH; 93%.

Mono protection of the diol 2 as a benzyl ether followed by Swern oxidation, gave the aldehyde 6, which reacted with $CH_3(CH_2)_{13}MgCl$ in the presence of CuBr SMe₂¹³ affording the adduct 7 with diastereoselectivity (7.1:1) in 49% yield. Protection of the secondary alcohol 7 as a MOM ether, and subsequent removal of the benzyl group by catalyic hydrogenation over Pd/C gave the bis-THF segment 8 in 93% yield.

The preparation of the other segment 15 is shown in Scheme 2. The epoxide 9¹⁴ was opened by lithium alkynylide 10 in the presence of $BF_3 OEt_2$ and the resulting alcohol was treated with MOMCl/*i*-Pr₂NEt to give 11. Aldol condensation of the enolate of 11 and aldehyde 12¹⁵

produced the compound 13 (mixture of diastereoisomers). Protection of the newly generated hydroxyl group in 13 as a MOM ether and treatment with 9% H_2SO_4 :THF (1:3) afforded the lactone 14.¹⁵ Bromination of the propargyl alcohol 14 gave the segment 15, which was then reacted with PPh₃ to afford the Wittig salt 16.

Scheme 2



Conditions: a) BF₃·OEt₂, THF, -78 °C; 83%. b) MOMCl, *i* -Pr₂NEt, CH₂Cl₂: 86%. c) LDA, THF, -78°C; then **12**; 80%. d) 9% H₂SO₄, THF; 65% (two steps). e) PPh₃, CBr₄, CH₂Cl₂: 89%. f) PPh₃, PhH, 87%.



Conditions: a) Swern oxidation. b) **16**, ^tBuOK, THF, -78 -0 $^{\circ}$ C; 32% (two steps). c) Pd/C, H₂, EtOH. d) DBU,THF; 56% (two steps). e) BF₃ OEt₂, DMS; 79%.

The coupling reaction between the aldehyde prepared from 8 in situ and the ylid prepared from 16 gave the enyne 17 (Z-isomer predominated) in 32% yield. Compound 17 was hydrogenated over Pd/C, and then treated with DBU to afford 18 in 56% yield. Deprotection of 18 with $BF_3 OEt_2$ gave 1 in 79% yield.

The spectral data (¹H and ¹³C nmr, HRMS) of the synthetic compound 1 are completely consistent with those reported for the title compound in literature.^{2, 3} However, the specific rotation is opposite to that reported. {Our synthetic compound 1: $[\alpha]_D^{20}$ -11.4 (c 0.70, CHCl₃), $[\alpha]_D^{26}$ -11.9 (c 0.43, CH₂Cl₂); Lit.² $[\alpha]_D$ +6.0 (c 0.05, CHCl₃); Lit.³ $[\alpha]_D$ +11.3 (c 1.00, CH₂Cl₂)}. In order to clarify this problem, we immediately synthesized diastereoisomer 19 (Figure 2) using the enantiomer of segment 8 made via the same procedures as those mentioned

above. We found that 19 has the same spectral data and close specific rotation as that reported in literature. { $[\alpha]_D^{24}$ +6.4 (c 0.36, CHCl₃); $[\alpha]_D^{25}$ +7.0 (c 0.10, CH₂Cl₂) }. Thus, this work strongly suggests the natural product has the opposite absolute configuration on the bis-THF unit to that reported in the literature.



In conclusion, we have developed an efficient procedure for the stereocontrolled synthesis of adjacent *trans/threo/trans* bis-THF ring units and a convenient route to couple this key intermediate with other building blocks. The first total synthesis of the title compound has been achieved in thirteen steps from the starting material **3**. In order to disclose the relationship between structure and biological activity, syntheses of asimilobin analogs are in progress.

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Reference and Notes

- 1. Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. Nat. Prod. Rep. 1996, 13, 275.
- 2. Woo, M. H.; Cho, K. Y.; Zhang, Y.; Zeng, L.; Gu, Z.-M.; McLaughlin, J. L. J. Nat. Prod. 1995, 58, 1533.
- 3. Zhang Y.; Zeng, L.; Woo, M.-H.; Gu, Z.-M.; Ye, Q.; Wu, F.-E.; McLaughlin, J. L. Heterocycles, 1995, 41, 1743.
- 4. Marshall, J. A.; Jiang, H. Tetrahedron Lett. 1998, 39, 1493 and references cited therein.
- 5. Hoye, T. R.; Ye, Z. J. Am. Chem. Soc. 1996, 118, 1801 and references cited therein.
- 6. Konno, H.; Makabe, H.; Tanaka, A.; Oritani, T.; Tetrahedron Lett. 1996, 37, 5393.
- 7. Makabe, H.; Tanaka, A.; Oritani, T. Heterocycles, 1996, 43, 2229 and references cited therein.
- 8. Figadère, B. Acc. Chem. Res., 1995, 28, 359 and references cited therein.
- 9. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Chem. Rev. 1994, 94, 2483.
- The ee of the resulting diol 4 {[α]_D²⁰ +11.6 (c 1.70, CH₂Cl₂)} is determined by comparing the specific optical rotation with its opposite enantiomer {[α]_D¹⁹ -11.1 (c 2.75, CH₂Cl₂); Lit. [α]_D -11.7 (c 1.5, CH₂Cl₂)} reported in literature [Vanhessche, K. P. M.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett.* 1994, *35*, 3469].
- 11. Inoki, S.; Mukaiyama, T. Chem. Lett. 1990, 67.
- 12. Wagner, H.; Koert, U. Angew. Chem. 1994, 106, 1939.
- 13. Mead, K.; Macdonald, T. L. J. Org. Chem. 1985, 50, 422.
- Vigneron, J. P.; Meric, R.; Larcheveque, M.; Debel, A.; Kunesch, G. Zagatti, P.; Gallois, M.; Tetrahedron Lett. 1982, 33, 5051.
- 15. Yao, Z.-J.; Wu, Y.-L. J. Org. Chem. 1995, 60, 1170.